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COMMENTARY

The cardiovascular risks of thiazide diuretics

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It is not surprising that a discipline as rapidly growing and changing as the management of hypertension should engender a number of controversies. These disagreements may have considerable medical, economic, and public health impact simply because there are so many millions of patients with hypertension involved. The purpose of this discussion is to present what some would consider controversial points of view concerning the safety of thiazide diuretics.

DOSE, VOLUME CHANGE, AND BLOOD PRESSURE REDUCTION WITH DIURETICS

There is a close association between volume reduction and the antihypertensive response to diuretics. Chlorothiazide causes a fall of approximately 10% in extracellular volume and 15% in plasma volume,[1,2] which incidentally is the same as the reduction associated with severe dietary restriction of sodium.[3,4]

The reduction in extracellular fluid volume is reflected in a loss of body weight of approximately 1 to 2 kg.[2,5] If weight loss does not occur, it is uncertain whether any reduction of blood pressure (BP) can be ascribed to the effects of the diuretic. MacGregor et al.[6] did not observe any reduction in body weight with small doses of hydrochlorothiazide, 12.5 and 25 mg/day, but there was a weight reduction with doses of 50 mg/day. Although some patients respond to 25 mg with a fall in BP, in other patients doses <50 mg/day would not be sufficient to lower volume and, possibly, BP effectively.

In a Veterans Administration Cooperative study,[7] 340 patients with mild hypertension received a dose of hydrochlorothiazide, 25 mg twice a day, initially that was increased as needed to 50 and then 100 mg twice a day. Fifty percent of those who achieved a diastolic BP <90 mm Hg did so with 25 mg twice a day (50 mg/day), 30% of these responders required 100 mg/day, and the remaining 20% of these responders needed 200 mg/day. Thus many of these patients required doses far in excess of 12.5 or 25 mg/day. Other studies have also found that the dose-response curve of hydrochlorothiazide does not remain flat in the small dose range, and considerably higher doses such as 100 mg/day are required in many patients.[8,9]

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Administering a diuretic plus a step 2 drug (similar to studies that claimed effectiveness of small doses of hydrochlorothiazide,[6,10,11] Magee and Freis[12] tested nadolol, 80 mg/day, plus various doses of hydrochlorothiazide, including 12.5, 25, and 50 mg/day. Each dose was given for 3 weeks with an intervening diuretic placebo period of 2 to 4 weeks. As compared with placebo, there was no reduction in BP with the 12.5 mg dose of hydrochlorothiazide. The 25 mg dose lowered systolic but not diastolic BP significantly, whereas the 50 mg dose lowered both significantly. Thus there were many patients whose diastolic BP was not well controlled with small doses <50 mg/day.

HYPOKALEMIA, EXTRACELLULAR AND INTRACELLULAR

One of the most widely held dogmas concerning the treatment of hypertension is that diuretic-induced hypokalemia must be avoided. As a result, sales of potassium salts and potassium-sparing diuretics have totalled over 250 million dollars per year.[13] Also, some investigators have reduced the doses of diuretics to very low levels, such as 6.25 or 12.5 mg hydrochlorothiazide per day.[10,11]

The extracellular hypokalemia caused by diuretics is not associated with a similar reduction in intracellular potassium. A review of the literature indicates that, with few exceptions, most investigators found that only minimal reductions (average 5% to 7%) in total body potassium stores occur after thiazides.[14] In contrast, the fall in extracellular potassium levels is much greater, averaging 20% below the pretreatment control level.[14] The large concentration gradient between extracellular and intracellular potassium is maintained by several active transport mechanisms, the most important of which is the sodium-potassium metabolic pump.[15] Because of these active transport mechanisms, extracellular hypokalemia can exist with little change in intracellular potassium concentrations.

In the presence of heart disease and especially in patients with congestive heart failure, there may be a reduction in myocardial intracellular potassium concentrations.[16] However, in the great majority of patients with hypertension who do not have overt heart disease there is no evidence that intracellular potassium levels are significantly reduced.[16] Hypomagnesemia also may occur after diuretic therapy,[17] although there is little evidence to implicate this biochemical change as a major cause of arrhythmias.

ECG MONITORING

Through the use of 24- or 48-hour continuous monitoring of the ECG, recent studies in patients with uncomplicated hypertension carried out by Papademetriou et al.[18] in our laboratory found no association between hypokalemia and ventricular arrhythmias. Monitoring was carried out before and after 4 weeks of therapy with hydrochlorothiazide, 50 mg twice a day, in 24 patients, 15 of whom became hypokalemic. In the hypokalemic group the mean plasma potassium level fell from 4.0 to 3.0 mEq/L. Before diuretic therapy premature ventricular beats (PVBs) averaged 7.1 per hour. Five patients had multifocal PVBs, one had couplets, and one had a four-beat run of ventricular tachycardia. After diuretic therapy the PVBs averaged 8.3 per hour. Three patients had multifocal PVBs and three had couplets, while none had ventricular tachycardia. Thus there was no essential difference in the incidence of arrhythmias before or after the induction of hypokalemia. Two other independent investigators have confirmed this finding.[19,20] For example, Lief et al.[19] conducted 48-hour continuous ECG monitoring in 13 patients with uncomplicated hypertension. Treatment with 100 mg hydrochlorothiazide per day for 1 to 6 months lowered plasma potassium levels to the range of 2.5 to 3.2 mEq/L. When monitoring was repeated at the end of the 6 months, the ECG did not reveal either increased or dangerous ectopy such as couplets or ventricular tachycardia. The increase in serum potassium to normal levels in patients with overt hypokalemia that resulted from potassium supplements or potassium-sparing diuretics also had no effect on ventricular arrhythmic activity.[21]

Two older studies[22,23] did report an association between cardiac arrhythmias and hypokalemia secondary to thiazides. Holland et al.[22] used 24-hour monitoring of the ECG before and after hydrochlorothiazide, 100 mg/day, but did not take into account that in the same individual the frequency of PVBs can vary over a wide range from one day to the next.[24] By including only patients with <6 PVBs per hour at baseline, Holland et al. increased the likelihood of finding increased arrhythmias on the second or hypokalemic recording by chance alone. The negative findings of Papademetriou et al.[18,21] and Leif et al.[19] were not based on the exclusion of patients with more than minimal PVBs. Although similarly designed to the study of Holland et al., the study of Madias et al.[20] did not confirm his results.

Hollifield and Slaton,[23] who also found an association between hypokalemia and cardiac arrhythmias after hydrochlorothiazide, 100 mg/day, did not use 24-hour monitoring but instead recorded the ECG during relatively short periods of exercise. These findings have not yet been confirmed.

The Medical Research Council of Great Britain trial

reported two contradictory studies.[25] An increased incidence of ventricular ectopy was noted in one subgroup of patients receiving long-term therapy with thiazides. However, these patients had no predose baseline recordings. In a second study patients were monitored both before and after therapy. Results indicated no increase in arrhythmias after thiazides. There was also no correlation between serum potassium levels and the frequency of ventricular arrhythmias in these patients without overt heart disease.

HYPOKALEMIA AND SUDDEN DEATH

The large Multiple Risk Factor Intervention Trial (MRFIT)[26,27] was a primary prevention trial intended to test the effects of a multifactorial intervention program, that included antihypertensive drugs, on death resulting from coronary heart disease. After 7 years morbidity did not differ significantly in the special intervention group who received drug therapy for hypertension (including 50 to 100 mg hydrochlorothiazide or chlorothalidone per day) and those who were referred to community health facilities where they received no or unknown therapy. A subgroup of intensive care patients who had minor ECG abnormalities had higher death rates from coronary heart disease than did the referred-care group with similar characteristics. This observation has been widely quoted as evidence that thiazides increase the incidence of fatal arrhythmias in a subgroup of patients with minor ECG abnormalities. The evidence is questionable, however, for several reasons. The most important reason is that the relationship between coronary deaths and thiazide diuretics was not an initial objective of the study, but was rather a part of a retrospective search for associations between a number of subgroups. As the authors of MRFIT report themselves state, evidence derived from such retrospective correlations can only be regarded as hypotheses that must be supported by other well-designed trials.[29]

Such confirmatory reports have not been forthcoming. For example, the Hypertension Detection and Follow-up Program (HDFP) included 1963 participants who had diastolic BP between 90 and 104 mm Hg and resting ECG abnormalities similar to the group with increased sudden death in the MRFIT. They found that rates for the major cardiovascular diseases were lower in the groups who received chlorthalidone, 50 mg/day. They concluded: "These HDFP findings, therefore, offer no support for the hypothesis raised in MRFIT that intensive diuretic therapy may increase the mortality rate of hypertensive patients with resting ECG abnormalities."[28] There was also no correlation in the MRFIT between either diuretic dosage or serum potassium levels and deaths from coronary heart disease.[26]

The evidence cited above is against the view that, in patients without heart disease, thiazide-induced hypokalemia causes increased cardiac arrhythmias including sudden death. Because of the fear of fatal arrhythmias, potassium replacement therapy may be overdone[1] and possibly could lead to serious consequences.[30]

HYPOKALEMIA AND ACUTE MYOCARDIAL INFARCTION

Many physicians are concerned that in the presence of acute myocardial infarction, fatal arrhythmias are more likely to develop if the patient had been receiving a thiazide diuretic. Not only is there a fall in plasma potassium levels after thiazide dosing, there is also a reduction resulting from the production of catecholamines that occurs in response to the stress associated with the acute event.[31] The resulting hypokalemia in the presence of increased susceptibility to arrhythmias secondary to the acute infarct could set the stage for ventricular fibrillation. If such were the case, however, one would expect a higher percentage of fatal myocardial infarctions and sudden death in patients receiving thiazide diuretics before the infarct than in those who do not receive diuretics. As indicated above, an increase in sudden death and myocardial infarction was found in a subgroup in the MRFIT. An insignificant increase also was found in the patients who received thiazides in the Oslo trial.[32]

Despite the higher coronary artery disease death rate in one subgroup, the MRFIT reported a 7% lower death rate for myocardial infarction in the total special intervention group. More importantly, most of the other therapeutic trials that have used thiazide diuretics as the basic therapy did not find an increase in sudden death or fatal myocardial infarction among the patients receiving the drug as compared with the control group. In fact, fatal myocardial infarction and sudden death was less frequent in the patients receiving thiazides than in the controls in most of the trials. Such was the experience of the Veterans Administration Study,[33] the Australian trial,[34] and the HDFP.[28] In each of these studies the ratio of the percentages of fatal infarcts to total infarcts was lower in the patients who received the drug than in the control patients, opposite to what one would expect if diuretics caused fatal arrhythmias in patients with acute myocardial infarction. If there is an increased susceptibility to arrhythmias induced by diuretics, as suggested by the MRFIT,[26] it is confined to only one subgroup of patients with minor ECG abnormalities. However, as has been shown by the HDFP data,[28] even these subgroup findings could not be confirmed.

As indicated above, except for one subgroup of the

MRFIT and an insignificant increase among the patients who received active drug in the Oslo trial, the other studies failed to indicate a rise in the number of deaths from coronary artery disease associated with thiazide diuretics. Thus the burden of evidence from the clinical trials indicates that thiazide diuretics do not increase the number of deaths in patients with hypertension who develop an acute myocardial infarction. There have been some reports of patients presenting at hospitals in whom there was an association between hypokalemia and malignant arrhythmias in the presence of acute myocardial infarction. Such reports were not well documented, however.[1] There was inadequate monitoring and lack of serum potassium level measurements immediately before the event. In fact, some levels were measured after the patients were resuscitated, which in itself could cause severe hypokalemia. Finally, patients taking digitalis were included in the studies even though digitalis is known to be associated with arrhythmias in the presence of hypokalemia.

Nordrehaug[35] recently reported on the relationship between hypokalemia, arrhythmias, and the early prognosis in 289 women and 785 men hospitalized with acute myocardial infarction. All patients had serum potassium levels determined on admission and the ECG was monitored continuously for the first 2 days. The study showed no significant increase in complete heart block, bundle branch block, grade 2 atrioventricular block, atrial fibrillation, PVBs, or ventricular tachycardia in patients with hypokalemia on admission to the hospital as compared with those who did not have hypokalemia. It should be noted that the patients received their drug therapy in a coronary care unit. If a causal relationship between hypokalemia and arrhythmias were to be accepted, it is possible that the hypokalemia might have affected the outcome differently if the patients were managed under less ideal circumstances. Also, hypokalemia on admission did not predict prognosis during the first 3 months after the infarct. Thus there was no correlation between either death or the incidence of arrhythmias and the presence of hypokalemia, with one exception of ventricular fibrillation.[36] As previously discussed, intracellular potassium levels may be decreased in the myocardium of patients with heart disease,[16] and this reduction may be further aggravated by diuretics. This relationship is controversial, however, as there may be other causes of ventricular fibrillation as indicated below.

In addition to diuretics, excess circulating catecholamines can also cause hypokalemia.[31] The excess of catecholamines usually occurs during the early stages of an acute myocardial infarction. In addition, catecholamines are known to induce arrhythmias independent of their hypokalemic effects. It is possible, therefore, that the hypokalemia in this instance may be only a marker for the presence of excess catecholamines that are producing ventricular fibrillation through some other mechanism.

Nordrehaug et al.[37] studied 60 patients who had received no prior drug therapy, including diuretics, before their acute myocardial infarction. Serum potassium levels correlated negatively with ventricular tachycardia. However, blood samples for the determination of potassium levels were drawn early, at an average of 3.8 hours after the onset of the infarct. This was much earlier than in a study[35] in which no correlation was found between serum potassium levels and ventricular tachycardia. Because in the latter study no patients were receiving a diuretic before the infarct, it seems most likely that hypokalemia was a reflection of the catecholamine level, which again could have caused ventricular tachycardia from arrhythmogenic effects of catecholamines other than their hypokalemic action.

Additional evidence against the prognostic importance of hypokalemia in acute myocardial infarction is provided by studies that show that the infusion of glucose, insulin, and potassium fail to reduce the incidence of ventricular tachycardia and fibrillation in patients with acute myocardial infarction.[38,39]

DIURETICS AND INCREASED SERUM CHOLESTEROL LEVELS

Another concern in the use of diuretics is that elevations in serum levels of cholesterol, although slight, might over a long period of time aggravate coronary heart disease. It was postulated that the protective effect of the BP lowering could be cancelled out by the rise in cholesterol levels.[40]

Serum cholesterol levels do rise modestly after thiazide diuretic dosing.[40,41] However, the elevation usually reverts back to pretreatment levels during long-term dosing. Except for one study,[42] serum cholesterol levels measured during the first few months of treatment were no longer elevated 1 or 2 years later.[43-47] Other studies documented the initial rise in cholesterol levels followed by the later fall. Alcazar et al.[45] observed the expected rise in cholesterol levels at 1 and 3 months after the start of hydrochlorothiazide dosing. Cholesterol levels returned to pretreatment levels at 6 months and remained there subsequently. The Veterans Administration study on hydrochlorothiazide vs. propranolol[46] also found serum cholesterol levels to be slightly elevated after 3 months of dosing, but by 12 months the cholesterol level had fallen to slightly below pretreatment

values. Using the data from HDFP, Williams et al.[47] also found a short-term increase followed by a long-term return to baseline. Thus according to practically all of the existing evidence, the elevation in serum cholesterol levels is only transient and, therefore, of no importance in the development of atherosclerosis.

CONCLUSIONS

The claim that diuretic-induced hypokalemia and increased serum cholesterol levels may be dangerous is not supported by recent evidence. These data indicate that (1) in the absence of digitalis and possibly overt heart disease, the hypokalemia is not associated with increased ventricular arrhythmias, and (2) the elevation in serum cholesterol levels reverts back to normal with long-term therapy. Thus the principle charges brought against the diuretics with respect to the heart appear to have little substance. The diuretics remain as our most valuable antihypertensive drugs, not only as single agents but also in the enhancement of antihypertensive effects of other drugs. To replace them with less effective drugs or to reduce their doses to marginally effective levels would only make the control of hypertension more difficult.

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